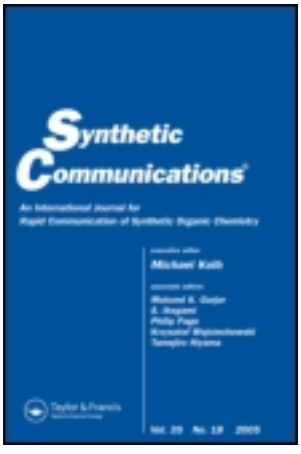

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Synthesis of Ribavirin Analogues Containing Amino-Acid Residues

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Synthesis of Ribavirin Analogues Containing Amino-Acid Residues

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Abstract: A convenient procedure for coupling 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose and 4-nitroimidazole was developed to obtain β-anomer as the major product. A novel category of nucleoside analogues with the introduction of natural L-amino acids to the base moiety were designed and synthesized to develop selective and effective antiviral agents.

Keywords: Amino acid, glycosidation, nucleoside, ribavirin

INTRODUCTION

Intensive efforts are underway worldwide to develop chemotherapeutic agents that have effective antiviral or antitumor activity, especially nucleoside analogues.[1] A number of these have been approved as effect therapeutic drugs or are at different phases of clinical trials. Among them, Ribavirin **1**, a broad-spectrum antiviral nucleoside with 3-carboxamide triazole base moiety, exhibits excellent antiviral activity.[2] On the other hand, recent research suggests that nucleoside analogues containing amino-acid residues would lead to significant biological activity,[3] because they could bind to target enzymes or other target proteins more easily and effectively than the natural nucleosides and other analogues.

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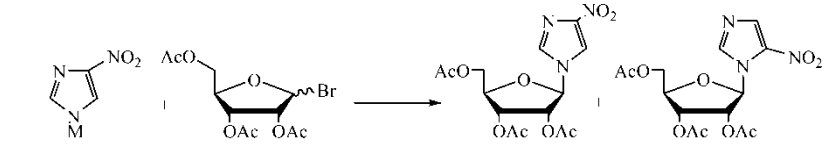
The combination of the previously mentioned information, the novel categories of nucleoside analogues **2** with an imidazole base moiety bearing amino-acid residue, and **3** with 4-amide imidazole base moiety were designed and synthesized (Fig. 1).

Compound **4** was conveniently reduced to **7** by hydrogenation. Because **7** is too unstable to separate,[4] it was therefore directly converted to **8** by condensation with formic acid or *N*-protected amino acids without further separation. Deprotection of the acetyl at the sugar moiety of **8a–e** with ammonia/methanol in almost quantitative yield, followed by deprotection of the benzyloxylcarbonyl at the nucleobase, gave target products **2a–e** smoothly, while deprotection of the acetyl at the sugar moiety of **7f–g** gave **3a–b** (Scheme 1). Many attempts had tried to remove *N*-protecting group benzyloxycarbonyl first, but failed. Only 2′,3′-acetyl at sugar moiety were removed and the resulting products were not the desired products.

The methods so far reported for preparing the key intermediate **4**, however, all appeared with some deficiencies. Chavis et al. and Humphries and Ramsden reported on the coupling of a metal salt of 4-nitroimidazole with 2,3,5-tri-*O*-acetyl-D-ribofuranose bromide, which gave a mixture of the isomers **4** and **5** (2:1) in moderate yield.[5,6]



More recently, Kumar et al. reported that coupling 2-nitro-1-trimethylsilylimidazole with some bromosugars gave almost quantitative yield; however, only α-anomer was obtained.[7]

Our initial attempt to prepare **3** was made by coupling 4-nitro-1-trimethylsilylimidazole and commercially available 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of $SnCl_4$ in acetonitrile, which gave a mixture of the isomers **4** and **6** (1:3) with the undesired α-anomer **6** as the major product (Scheme 2). Drawing inspiration from Alauddin et al.'s

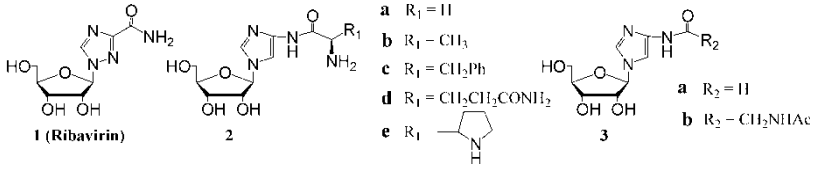
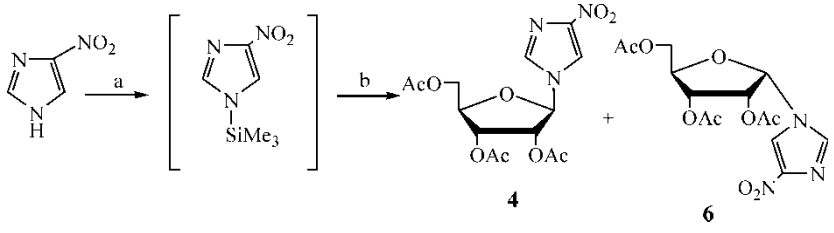


Figure 1. Ribavirin and target molecule.

Scheme 1. a) 1 atm H_2, 5% Pd/C, acetonitrile; b) formic acid or *N*-protected amino acids, DCC, acetonitrile; c) NH_3/CH_3OH, almost quantitative; d) 10% Pd/C, H_2, CH_3OH. Cbz = $COOCH_2Ph$.



Scheme 2. a) HMDS/$(NH_4)_2SO_4$, reflux; b) tetra-*O*-acetylribofuranose, $SnCl_4$, $ClCH_2CH_2Cl$, 90%.

recent discovery[8] and the addition of our own discovery, we finally carried out the coupling reaction in 1,2-dichloroethane instead of acetonitrile in the presence of $SnCl_4$ and a catalytic amount of $MgSO_4$. The β-anomer **4** turned out to be the major product (β-anomer 67.5%, α-anomer 22.5%, $\beta/\alpha = 3{:}1$) and can be easily separated by recrystallization.[†]

In conclusion, 1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)-4-nitroimidazole **4** was prepared as the major product by coupling 4-nitro-1-trimethylsilylimidazole and commercially available 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of $SnCl_4$ and $MgSO_4$. A series of ribavirin analogues was also synthesized.

EXPERIMENTAL

Melting points were determined with an XT-4 apparatus and are uncorrected. The ^{1}HNMR spectra were measured with Bruker AV-300 and AV-500 spectrometers. The IR spectra were determiined with a Brucker Vetor 22 spectrometer. A P-E240C apparatus was used for elemental analysis. All chemicals were analytically pure. 1,2-Dichoroethane was dried by anhydrous magnsium sulfate and distilled.

General Procedure for 4-Nitroimidazole Glycosidation

4-Nitroimidazole (2.346 g, 20.75 mmol) was refluxed with 70 ml HMDS and a catalytic amount of $(NH_4)_2SO_4$ until a clear solution was obtained (in about 4 h). The excess of HMDS was removed in vacuo. The silyated base was dissolved in anhydrous 1,2-dichloroethane (180 ml). A solution of

[†]The ratio was obtained by chromatography and HPLC, which used a C_{18} reverse-phase analytical column and an MeCN/H_2O solvent system (MeCN/H_2O = 2:7) as eluent. The product β appeared first at 12.967 min in the HPLC, and the compound α emerged at 17.938 min.

1,2,3,5-tetra-*O*-acetylribofuranose (5.279 g, 16.60 mmol) in 50 ml 1,2-dichloroethane and $MgSO_4$ (0.2 eq) were added at rt. Then, $SnCl_4$ (2.95 ml, 25.10 mmol) in 10 ml 1,2-dichloroethane was added dropwise below 0°C at the nitrogen atmosphere. The mixture was stirred at rt for 8–10 h. TLC showed that the reaction had completed; the reaction mixture was diluted with CH_2Cl_2 and quenched with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 ml). The combined organic phases were washed with water, dried over $MgSO_4$, and concentrated in vacuo. The isomers of the product were separated by column chromatography (eluent: petroleum ether ethyl acetate = 2:1) to give **4** (4.157 g, 67.5%) and **6** (1.386 g, 22.5%). The structures of compounds **4** and **6** were determined by NOE of ^{1}H NMR. In compound **6**, 1′-H had a plus of 7.67% when 2′-H was irradiated. While in compound **4**, 1′-H had no plus when 2′-H was irradiated. Compound **4**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.06 (s, 1H, 2-H), 7.72 (s, 1H, 5-H), 5.87 (d, J = 4.2 Hz, 1H, 1′-H), 5.34 (dd, J = 5.2, 4.2 Hz, 1H, 2′-H), 5.30 (t, J = 5.2 Hz, 1H, 3′-H), 4.53 (m, 1H, 4′-H), 4.40 (d, J = 2.5 Hz, 2H, 5′-H), 2.20 (s, 3H, CH_3CO-), 2.16 (2s, 6H, 2 × CH_3CO-). Compound **6**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.13 (s, 1H, 2-H), 8.06 (s, 1H, 5-H), 6.48 (s, 1H, 1′-H), 5.54 (d, J = 2.5 Hz, 1H, 2′-H), 5.34 (dd, J = 5.1, 2.5 Hz, 1H, 3′-H), 4.50 (dd, J = 5.1, 2.7 Hz, 1H, 4′-H), 4.43 (d, J = 2.7 Hz, 2H, 5′-H), 2.18 (2s, 6H, 2 × CH_3CO-), 2.08 (s, 3H, CH_3CO-).

General Procedure for the Preparation of 8a–g

1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)-4-nitroimidazole **4** was dissolved in anhydrous acetonitrile and reduced with 1 atm hydrogen in the presence of 5% Pd/C for 2–4 h at rt. When TLC showed that the reaction had completed, formic acid or *N*-protected amino acid (1.2 equiv.) was added, and the mixture was cooled to −5 to 10°C. N,N′-Dicyclohexylcarbodiimide (DCC) (1.5 equiv.) was added and stirred for 2–3 h, and then standed at rt overnight. The catalysts were removed by filtration. The product was purified by column chromatography (eluent: range from EtOAc to EtOAc/EtOH = 10:1).

4-*N*-[2-(*N*-benzyloxylcarbonylamino)-acetyl]amino-1-(β-D-2,3,5-tri-*O*-acetyl-ribofuranosyl)imidazole (**8a**). Yield: 70%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (s, 1H, 2-H), 7.59 (s, 1H, 5-H), 7.27–7.50 (m, 5H, Ar-H), 6.02 (d, J = 5.4 Hz, 1H, 1′-H), 5.53 (t, J = 5.4 Hz, 1H, 2′-H), 5.48 (dd, J = 3.6, 1.8 Hz, 1H, 3′-H), 5.12 (s, 2H, -OCH_2Ph), 4.47 (dd, J = 3.0, 3.6 Hz, 1H, 4′-H), 4.38 (d, J = 4.4 Hz, 2H, 5′-H), 4.03 (s, 2H, $NHCH_2CO$-), 2.20 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.4, 20.6, 20.8, 44.5, 63.1, 67.2, 70.9, 74.5, 80.7, 88.4, 104.2, 128.6, 128.8, 132.4, 136.4, 138.3, 156.7, 166.5, 169.4, 169.6, 170.7; IR (KBr, cm^{-1}) 3332 (NHCO), 1747 (COO-), 1667 (CONH).

4-*N*-[(s)-2-(*N*-benzyloxylcarbonylamino)-propionyl]amino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)imidazole (**8b**). Yield: 65%. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 7.73 (s, 1H, 2-H), 7.61 (s, 1H, 5-H), 7.20–7.40 (m, 5H, Ar-H), 6.00 (d, J = 5.6 Hz, 1H, 1′-H), 5.54 (t, J = 5.6 Hz, 1H, 2′-H), 5.47 (dd, J = 3.6, 1.8 Hz, 1H, 3′-H), 5.08 (s, 2H, OCH_2Ph), 4.47 (m, 2H, 4′-H and NHCHRCO-), 4.37 (d, J = 2.9 Hz, 2H, 5′-H), 2.20 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 1.43 (d, J = 7.1 Hz, 3H, -CH_3); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 18.7, 20.3, 20.5, 20.8, 51.4, 64.0, 66.9, 71.6, 75.0, 81.2, 88.7, 104.3, 128.6, 129.2, 134.1, 138.0, 139.5, 156.9, 170.2, 170.4, 170.8, 171.1; IR (KBr, cm^{-1}) 3317 (NHCO), 1747 (COO-), 1657 (CONH).

4-*N*-[(s)-2-(*N*-benzyloxylcarbonylamino)-3-phenyl-propionyl]amino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)imidazole (**8c**). Yield: 56%. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 7.77 (s, 1H, 2-H), 7.66 (s, 1H, 5-H), 7.08–7.37 (m, 10H, Ar-H), 6.01 (d, J = 5.4 Hz, 1H, 1′-H), 5.57 (t, J = 5.4 Hz, 1H, 2′-H), 5.48 (dd, J = 3.6, 1.8 Hz, 1H, 3′-H), 5.02 (s, 2H, OCH_2Ph), 4.74 (m, 1H, NHCHRCO), 4.48 (dd, J = 3.0, 3.2 Hz, 1H, 4′-H), 4.37 (d, J = 4.4 Hz, 2H, 5′-H), 3.24 (dd, J = 9.4, 4.1 Hz, 1H, -CH_2Ph), 3.03 (dd, J = 9.4, 4.1 Hz, 1H, −CH_2Ph), 2.18 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 20.3, 20.5, 20.8, 38.9, 57.1, 60.6, 64.0, 66.7, 71.5, 74.9, 81.1, 88.6, 104.5, 127.3, 128.4, 128.5, 129.0, 129.1, 130.1, 134.1, 137.8, 138.2, 139.3, 157.0, 169.6, 170.1, 170.4, 171.0; IR(KBr, cm^{-1}) 3330 (NHCO), 1749 (COO-), 1660 (CONH).

4-*N*-[(s)-2-(*N*-benzyloxylcarbonylamino)-4-amido-butyryl]amino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)imidazole (**8d**). Yield: 54%. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 7.77 (s, 1H, 2-H), 7.63 (s, 1H, 5-H), 7.20–7.36 (m, 5H, Ar-H), 6.00 (d, J = 5.7 Hz, 1H, 1′-H), 5.54 (t, J = 5.4 Hz, 1H, 2′-H), 5.47 (dd, J = 3.6, 1.8 Hz, 1H, 3′-H), 5.08 (s, 2H, OCH_2Ph), 4.47 (dd, J = 3.0, 9.5 Hz, 2H, 4′-H and NHCHRCO-), 4.37 (d, J = 2.0 Hz, 2H, 5′-H), 2.40 (d, J = 2.20 Hz, 2H, β-CH_2), 2.17 (s, 3H), 2.11 (s, 3H), 2.06 (m, 5H, CH_3CO- and γ-CH_2); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 19.5, 19.7, 20.0, 28.0, 31.3, 54.8, 63.1, 66.1, 70.7, 74.1, 80.3, 87.9, 103.7, 127.7, 128.3, 133.4, 137.0, 138.5, 138.6, 156.4, 169.3, 169.4, 169.7, 170.4, 172.7, 175.3; IR (KBr, cm^{-1}) 3339 (NHCO), 1748 (COO-), 1672 (CONH).

4-*N*-[(s)-(*N*-benzyloxylcarbonylpyrrolidine)-2-carbonyl]amino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)imidazole (**8e**). Yield: 48%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (s, 1H, 2-H), 7.45 (s, 1H, 5-H), 7.15–7.35 (m, 5H, Ar-H), 5.75 (d, J = 5.9 Hz, 1H, 1′-H), 5.38 (m, 2H, 2′-H, 3′-H), 5.12 (s, 2H, OCH_2Ph), 4.47 (m, 2H, 4′-H and NCHRCO-), 4.33 (d, J = 4.2 Hz, 2H, 5′-H), 3.55 (m, 2H, RCH_2N), 2.22 (s, 3H), 2.13 (s, 3H), 2.07 (s, 3H), 1.85–2.03 (m, 4H, β-, γ-CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.4, 20.6, 20.9, 23.6, 29.4, 47.4, 61.1, 63.2, 67.6, 70.9, 74.7, 80.6, 88.3, 104.0, 128.1, 128.6,

132.3, 136.4, 138.3, 156.7, 167.6, 169.3, 169.6, 170.6; IR (KBr, cm^{-1}) 3288 (NHCO), 1749 (COO-), 1698 (CONH).

4-*N*-Formylamino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl)imidazole (**8f**). Yield: 83%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H, HCO −), 7.56 (s, 1H, 2-H), 7.49 (s, 1H, 5-H), 5.77 (d, J = 4.7 Hz, 1H, 1′-H), 5.40 (m, 2H, 2′,3′-H), 4.38 (d, J = 2.8 Hz, 1H, 4′-H), 4.32 (d, J = 2.8 Hz, 2H, 5′-H), 2.21 (s, 3H), 2.11 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.5, 20.7, 20.8, 63.1, 70.8, 74.7, 80.6, 88.4, 104.7, 132.3, 137.9, 157.8, 169.5, 169.7, 170.8; IR (KBr, cm^{-1}) 3300 (NHCO), 1748 (COO-), 1690 (CONH).

4-*N*-[2-(*N*-Acetylamino)-acetyl]amino-1-(β-D-2,3,5-tri-*O*-acetylribofuranosyl) imidazole (**8g**).Yield: 61%. ^{1}H NMR (CD_3COCD_3, 300 MHz) δ 7.74 (s, 1H, 2-H), 7.58 (s, 1H, 5-H), 6.00 (d, J = 5.6 Hz, 1H, 1′-H), 5.53 (t, J = 5.6 Hz, 1H, 2′-H), 5.45 (dd, J = 3.6, 1.8 Hz, 1H, 3′-H), 4.47 (dd, J = 3.0, 3.6 Hz, 1H, 4′-H), 4.36 (d, J = 3.0 Hz, 2H, 5′-H), 4.03 (s, 2H, $NHCH_2CO$), 2.20 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.4, 20.6, 20.9, 23.0, 43.0, 63.2, 70.8, 74.5, 80.7, 88.4, 104.2, 132.3, 137.9, 166.4, 169.5, 169.7, 170.7, 171; IR (KBr, cm^{-1}) 3285 (NHCO), 1748 (COO-), 1656 (CONH).

General Procedure for Deprotection

Compound **8** was dissolved in methanol and reacted with NH_3 for 24–48 h. The solvent was evaporated in vacuo. The product of **8a–e** was dried in vacuo, then dissolved in anhydrous methanol and reduced with 1 atm hydrogen in the presence of 10% Pd/C (10–20% of **8**, w/w). The catalyst was removed, and the product was purified by chromatography (eluent: range from EtOAc EtOH = 1:8 to EtOH).

4-*N*-Formylamino-1-β-D-ribofuranosylimidazole (**3a**). Almost quantitive. Oil. ^{1}H NMR (D_2O, 300 MHz) δ 8.21 (s, 1H, HCO −), 7.76 (s, 1H, 2-H), 7.47 (s, 1H, 5-H), 5.74 (d, J = 5.4 Hz, 1H, 1′-H), 4.45 (t, J = 5.3 Hz, 1H, 2′-H), 4.31 (t, J = 4.6 Hz, 1H, 3′-H), 4.16 (dd, J = 4.0, 3.8 Hz, 1H, 4′-H), 3.72–3.83 (m, 2H, 5′-H); ^{13}CNMR (D_2O, 75 MHz) δ 60.9, 69.9, 74.5, 84.5, 89.4, 105.9, 133.7, 134.7, 160.8; IR (KBr, cm^{-1}) 3288 (OH, NHCO), 1668 (CONH); Anal. calcd. for $C_9H_{13}N_3O_5$: C, 44.45; H, 5.39; N, 17.28. Found: C, 44.19; H, 5.13; N, 17.03.

4-*N*-[2-(*N*-Acetylamino)-acetyl]amino-1-β-D-ribofuranosylimidazole (**3b**). Almost quantitive. White solid. Mp: 200.4–201.0°C. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.68 (s, 1H, 2-H), 7.34 (s, 1H, 5-H), 5.49 (d, J = 5.9 Hz, 1H, 1′-H), 4.11 (m, 1H, 2′-H), 4.00 (m, 1H, 3′-H), 3.86 (d, J = 3.3 Hz, 1H,

4′-H), 3.82 (d, J = 5.7 Hz, 2H, $NHCH_2CO$), 3.52 (t, J = 4.6 Hz, 2H, 5′-H), 1.86 (s, 3H, CH_3CO-); ^{13}CNMR (DMSO-d_6, 75 MHz) δ 22.4, 42.0, 61.4, 70.5, 75.1, 85.2, 89.6, 103.8, 132.9, 137.9, 166.2, 169.6; IR (KBr, cm^{-1}) 3276 (OH, NHCO), 1663 (CONH), 1638 (CONH); Anal. calcd. for $C_{12}H_{18}N_4O_6$: C, 45.86; H, 5.77; N, 17.83. Found: C, 45.61; H, 5.54; N, 17.59.

4-*N*-(2-amino-acetyl)amino-1-β-D-ribofuranosylimidazole (**2a**). Yield: 70%. Slightly yellow solid. Mp: 202.5°C (decomp.). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.67 (s, 1H, 2-H), 7.36 (s, 1H, 5-H), 5.48 (d, J = 4.4 Hz, 1H, 1′-H), 4.11 (t, J = 4.2 Hz, 1H, 2′-H), 4.00 (dd, J = 3.3, 2.9 Hz, 1H, 3′-H), 3.86 (d, J = 2.8 Hz, 1H, 4′-H), 3.54 (m, 2H, 5′-H), 3.22 (d, J = 5.5 Hz, 2H, NH_2CH_2CO); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 44.5, 61.4, 70.4, 75.0, 85.2, 89.6, 103.5, 132.9, 137.7, 170.2; IR (KBr, cm^{-1}) 3356 (OH, NHCO), 1675 (CONH); Anal. calcd. for $C_{10}H_{16}N_4O_5$: C, 44.12; H, 5.92; N, 20.58. Found: C, 43.88; H, 5.75; N, 20.30.

4-*N*-[(s)-2-amino-propionyl]amino-1-β-D-ribofuranosylimidazole (**2b**). Yield: 65%. White solid. Mp: 207.5°C (decomp.). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.69 (s, 1H, 2-H), 7.38 (s, 1H, 5-H), 5.50 (d, J = 5.6 Hz, 1H, 1′-H), 4.13 (dd, J = 4.9, 5.3 Hz, 1H, 2′-H), 4.02 (d, J = 2.8 Hz, 1H, 3′-H), 3.88 (d, J = 2.9 Hz, 1H, 4′-H), 3.40–3.60 (m, 3H, 5′-H and NHCHRCO), 1.20 (d, J = 6.6 Hz, 3H, -CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 18.8, 49.9, 61.5, 70.5, 75.2, 85.3, 89.7, 103.7, 133.0, 137.9, 171.7; IR (KBr, cm^{-1}) 3271 (OH, NHCO), 1682 (CONH); Anal. calcd. for $C_{11}H_{18}N_4O_5$: C, 46.15; H, 6.34; N, 19.57. Found: C, 45.92; H, 6.07; N, 19.30.

4-*N*-[(s)-2-amino-3-phenyl-propionyl]amino-1-β-D-ribofuranosylimidazole (**2c**). Yield: 52%. Yellow solid. Mp: 210.5°C (decomp.). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.69 (s, 1H, 2-H), 7.40 (s, 1H, 5-H), 7.15–7.35 (m, 5H, Ar-H), 5.50 (d, J = 5.8 Hz, 1H, 1′-H), 4.14 (dd, J = 5.1, 5.3 Hz, 1H, 2′-H), 4.01 (d, J = 4.0 Hz, 1H, 3′-H), 3.87 (d, J = 3.0 Hz, 1H, 4′-H), 3.42–3.65 (m, 3H, 5′-H and NHCHRCO), 3.01 (m, 1H, -CH_2Ph), 2.67 (m, 1H, -CH_2Ph); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 40.7, 55.8, 61.4, 70.4, 75.0, 85.2, 89.6, 103.7, 126.1, 128.1, 129.3, 133.0, 137.8, 138.5, 171.4; IR (KBr, cm^{-1}) 3337 (OH, NHCO), 1673 (CONH); Anal. calcd. for $C_{17}H_{22}N_4O_5$: C, 56.35; H, 6.12; N, 15.46. Found: C, 56.09; H, 5.86; N, 15.20.

4-*N*-[(s)-4-amido-2-amino-butyryl]amino-1-β-D-ribofuranosylimidazole (**2d**). Yield: 57%. White solid. Mp: 247.2°C (decomp.). ^{1}H NMR (D_2O, 500 MHz) δ 7.69 (s, 1H, 2-H), 7.43 (s, 1H, 5-H), 5.66 (d, J = 5.6 Hz, 1H, 1′-H), 4.41 (m, 1H, 2′-H), 4.36 (t, J = 5.4 Hz, 1H, 3′-H), 4.22 (dd, J = 4.6, 4.2 Hz, 1H, NHCHRCO), 4.08 (d, J = 3.5 Hz, 1H, 4′-H), 3.65–3.78 (m, 2H, 5′-H), 2.51 (m, 1H, β-CH_2), 2.40 (m, 2H, γ-CH_2), 2.08 (m, 1H, β-CH_2); ^{13}C NMR (D_2O, 125 MHz) δ 25.1, 29.2, 56.9, 61.1, 70.2, 74.7, 84.8, 89.6,

106.6, 134.4, 135.8, 172.5, 182.3; IR (KBr, cm^{-1}) 3460, 3386 (OH, NHCO), 1679 (CONH); Anal. calcd. for $C_{13}H_{21}N_5O_6$: C, 45.48; H, 6.16; N, 20.40. Found: C, 45.22; H, 5.88; N, 20.27.

4-*N*-[(s)-pyrrolidine-2-carbonyl]amino-1-β-D-ribofuranosylimidazole (**2e**). Yield: 55%. White solid. Mp: 205.2°C (decomp.). ^{1}H NMR (D_2O, 300 MHz) δ 7.68 (s, 1H, 2-H), 7.35 (s, 1H, 5-H), 5.65 (d, J = 5.7 Hz, 1H, 1′-H), 4.37 (t, J = 5.4 Hz, 1H, 2′-H), 4.22 (dd, J = 3.9, 5.1 Hz, 1H, 3′-H), 4.08 (t, J = 3.7 Hz, 1H, 4′-H), 3.94 (m, 1H, NHCHRCO), 3.65-3.78 (m, 2H, 5′-H), 3.01 (m, 2H, $NHCH_2R$), 2.18 (m, 1H, β-CH_2), 1.74–1.86 (m, 3H, β-CH_2 and γ-CH_2); ^{13}C NMR (D_2O, 75 MHz) δ 23.5, 29.4, 46.2, 59.6, 60.9, 69.9, 74.5, 84.6, 89.4, 106.1, 134.1, 135.4, 167.6; IR (KBr, cm^{-1}) 3376 (OH, NHCO), 1682 (CONH); Anal. calcd. for $C_{13}H_{20}N_4O_5$: C, 49.99; H, 6.45; N, 17.94. Found: C, 49.74; H, 6.20; N, 17.78.

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